REMARKS

Claims 22, 24, 25, 28, 33-36, 38, 41-43, 45 and 48 are pending in this application. Claims 22, 24, 25, 28, 33-36, 38, 41-43, 45 and 48 are rejected. Claim 33 is allowed. Applicants hereby amend claims 22, 34, 35 and 42, and add new claims 49-55. Support for new claims 49-55 exists throughout the specification as filed. No new matter has been added.

Applicants would like to thank the Examiner for the withdrawal of the previous rejections under 35 U.S.C. §112 and §102(e).

Claim Rejections – 35 U.S.C. §112

Applicants would like to thank the Examiner for the helpful interview that was conducted on February 16, 2006, The amendments and following remarks are submitted pursuant to those discussions.

Claim Rejections – 35 U.S.C. §112

Claim 34

The Examiner has rejected Claim 34 as failing to comply with the written description requirement. Specifically, the Examiner states that "...the specification and claims, as originally filed, does not appear to support the limitation 'in the absence of said maleimide group'". Applicants disagree, but in order to facilitate prosecution Applicants hereby amend Claim 34 to remove the above limitation. In light of this amendment to claim 34, Applicants respectfully request this ground for rejection be withdrawn.

Claims 35-36, 38, 41, 42-43, 45 and 48

The Examiner has also rejected claims 35-36, 38, 41, 42-43, 45 and 48 because "...the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims."

Specifically, the Examiner states that "The instant specification is not enabling for claims drawn to a conjugate of formula: blood component-reactive group-peptide, wherein said peptide is a kringle 5 peptide comprising SEQ ID NO: 8, reactive group is a succinimidyl group bonded to an amino group, a hydroxyl group or a thiol group of a blood component by means of a stable covalent bond." The Examiner further states that "a reaction between a kringle 5 peptide comprising an amino acid sequence of SEQ ID NO: 8 modified with a succinimidyl group and a blood protein does not appear to result in the conjugate as presently claimed."

Applicants thank the Examiner for pointing out the inconsistency in the claim language, and amend claim 35 address this issue. Claim 35 as amended reads: "A conjugate comprising a modified kringle 5 peptide covalently bonded to a blood component, where said modified kringle 5 peptide comprises SEQ ID NO: 8 and a reactive group coupled thereto, said reactive group reacting with an amino group, a hydroxyl group or a thiol group on a blood component to form a covalent bond, wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group."

This amended claim finds support in and is enabled by the specification as filed. Support exists at page 15, lines 1-7; page 17, lines 4-16; and page 35, lines 20-29 of the specification as filed. As such, claims 35-36, 38, 41, 42-43, 45 and 48 meet the requirements of 35 U.S.C. §112.

Applicants respectfully request this ground of rejection be withdrawn.

Claim Rejections – 35 U.S.C. §102(b)

The Examiner has rejected claims 22 and 24 as being anticipated by Davidson et al. (WO 97/41824). Davidson et al. discloses a kringle 5 peptide, shown on page 43, example 5, with an acetyl group at the N-terminus. With the exception of the acetyl group, the sequence of the kringle 5 peptide is the same as the presently claimed kringle 5 peptide of SEQ ID NO: 8. However, the "**modified** kringle 5 peptide" (emphasis added) of claim 22 as amended comprises "SEQ ID NO:8 **and a reactive group** coupled thereto, said reactive group reacting with an amino group, a hydroxyl group, or a thiol group on a blood component to form a stable covalent bond, **wherein said reactive**

group is selected from the group consisting of succinimidyl and maleimido groups." (emphasis added) Davidson et al does not teach or suggest modifying the kringle 5 peptide to contain a reactive group.

The Examiner cites page 12, lines 20-26 of the WO application, which states:

> "The term 'activated ester derivative' as used herein refers to acid halides such as acid chlorides, and activated esters including, but not limited to, formic acid and acetic acid derived anhydrides, anhydrides derived from alkoxycarbonyl halides such as isobutyloxycarbonylchloride, and the like, N-hydroxysuccinimide derived esters..."

This passage provides a definition of an activated ester derivative, but does not teach that a kringle 5 peptide may be modified to include an activated ester derivative. This passage is the only mention of an activated ester derivative in the entire specification. Therefore, there is no teaching in Davidson et al. that a kringle 5 peptide may be modified to include an activated ester derivative.

The Examiner further cites page 13, line 1 to page 15, line 36, and page 43, Example 5 as providing methods of manufacturing the anticipated composition. The passage beginning at page 13, line 1 and ending at page 15, line 36 describes amino acids which can be used in the invention, and lists embodiments of particular structures, such as B-C-X, wherein B is a part of SEQ ID NO: 1, C is a 4mer peptide, and X is a 9 or 12mer peptide. Nowhere within this passage is there any description of manufacturing the claimed composition, namely "a modified kringle 5 peptide wherein said kringle 5 peptide comprises SEQ ID NO: 8 and a reactive group coupled to said kringle 5 peptide said reactive group reacting with an amino group, a hydroxyl group, or a thiol group on a blood component to form a stable covalent bond, wherein said reactive group is selected from the group consisting of succinimidyl and maleimido groups." Applicants were unable to find such a teaching anywhere in Davidson et al.

The Examiner further states: "Thus, while Davidson et al. does not explicitly teach that the modified kringle 5 peptide having a N-hydroxysuccinimide derived activated ester reacts with

an amino group or a hydroxyl group on a blood component to form a stable covalent bond, the claimed functional limitation would be an inherent property of the referenced method since the specification discusses (page 11, lines 5-20) that primary amines are the principal targets of NHS esters, wherein accessible α-amine esters present on the N-termini of proteins react with NHS esters. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the active steps of the prior arts disclosure."

The referenced passage on page 11, lines 5-20 describes representative carboxy protecting groups, and does not teach that primary amines are the principal targets of NHS esters. Applicants were unable to find any such teaching in Davidson. Since the Examiner agrees that "Davidson et al. does not explicitly teach that the modified kringle 5 peptide having a N-hydroxysuccinimide derived activated ester reacts with an amino group or a hydroxyl group on a blood component to form a stable covalent bond", and there is no teaching that primary amines are the principal targets of NHS esters, Applicants fail to see how "the claimed functional limitation would be an inherent property of the referenced method".

Applicants assert that the Davidson, et al. reference does not contain all of the limitations of independent claim 22 or dependent claim 24, namely it does not contain any explicit or inherent teaching that a kringle 5 peptide can be modified to contain a reactive group, wherein said reactive group is selected from the group consisting of succinimidyl and maleimide groups. There is also no teaching that the modified kringle 5 peptide can react *in vivo* with a blood component. In light of these arguments and amendments, Applicants assert that the Davidson, et al. reference does not anticipate claims 22 or 24, and respectfully request the withdrawal of this ground of rejection.

Claim Rejections – 35 U.S.C. §103(a)

Claims 22, 24-25, 35-36, 38, 41-43, 45 and 48

The Examiner has rejected claims 22, 24-25, 35-36, 38, 41-43, 45 and 48 as being unpatentable over Davidson et al. in combination with Peeters et al (J. Immunol Methods 1989; 120: 133-143) in view of Humphries et al. (J. Tissue Culture Methods 1994; 16: 239-242). Specifically,

the Examiner states: "It would have been *prima facie* obvious to one of skill in the art at the time the invention was made to use MHS instead of glutaraldehyde to link a carrier protein, such as bovine serum albumin, with a kringle 5 peptide in view of the teachings of Peeters et al."

In order to make a *prima facie* case of obviousness, three criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (MPEP 2142). Applicants contend that Davidson, Peeters and Humphries, when combined, do not teach or suggest all of the claim limitations. Specifically, the references when combined do not teach or suggest a modified kringle 5 peptide wherein said kringle 5 peptide comprises SEQ ID NO: 8 and **a reactive group, wherein said reactive group is a succinimidyl-containing group or maleimido-containing group**, as claimed in independent claims 22 and 35. (emphasis added)

The Examiner states: "Davidson et al. disclose, as discussed above for claims 22 and 24, a kringle 5 peptide or ester thereof having an amino acid sequence which appears to be 100% identical to the currently claimed modified peptide comprising SEQ ID NO: 8, wherein the peptide may be modified to include an activated ester derivative such as N-hydroxysuccinimide derived esters (page 12, lines 20-26)." As discussed above, page 20, lines 20-26 of Davidson, et al. provides a definition of an activated ester derivative, but does not provide any teaching that a kringle 5 peptide could be modified to include an activated ester derivative. Therefore, there is no teaching to support the claimed limitation of a reactive group, wherein said reactive group is selected from the group consisting of succinimidyl and maleimido groups.

The Examiner continues: "The WO document also discloses (page 13, line 1-page 15, line 6 and Example 5) methods of manufacturing the anticipated composition including a kringle 5 peptide and derivatives and analogs thereof." As discussed above, the cited pages do not contain any description of manufacturing the composition of claim 22, "a modified kringle 5 peptide wherein said kringle 5 peptide comprises SEQ ID NO:8 and **a reactive group** coupled thereto, said reactive group reacting with an amino group, a hydroxyl group, or a thiol group on a blood component to form a stable covalent bond, **wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group**." (Emphasis added) Applicants were unable to find such a teaching

anywhere in Davidson et al. Therefore there is no teaching or suggestion to support the claimed limitation of a reactive group, wherein said reactive group is selected from the group consisting of succinimidyl and maleimido groups.

The Examiner continues: "Moreover, Davidson et al. teach coupling the kringle 5 protein with carrier proteins to form a conjugate (page 35, lines 22-30). This section states:

> "Conjugates include enzymes, carrier proteins, cytotoxic agents, fluorescent, chemiluminescent and bioluminescent molecules which are used to facilitate the testing of the ability of compounds containing kringle 5 peptide fragments to bind kringle 5 antisera, detect cell types which possess a kringle 5 peptide fragment receptor or aid in purification of kringle 5 peptide fragments."

There is no teaching to support the claimed limitation of a kringle 5 peptide comprising a reactive group, wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group.

Finally, the Examiner states: "For Example, the WO document teaches using glutaraldehyde to link kringle 5 peptide fragments containing a lysine with bovine serum albumin (page 36, lines 8-9)." Glutaradelhyde is the only linkage described, and there is no teaching of using a succinimidyl or maleimide group as a reactive group to form the conjugate.

Therefore, Davidson, et al. does not describe the claimed limitation of a kringle 5 peptide comprising a reactive group, wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group.

Peeters, et al. teaches the use of four hetero bifunctional groups for coupling a protein to a peptide. These bifunctional groups are first reacted with BSA, and then the BSA-reactive group conjugate is reacted with a peptide of interest to form a BSA-reactive group-peptide conjugate. There is no teaching of a modified peptide comprising a reactive group, wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group.

Therefore, neither Davidson nor Peeters teach the claimed limitation of a kringle 5 peptide comprising a reactive group, wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group. Humphries, et al. also teach reaction of hetero bifunctional cross-linkers to a carrier protein (one example is BSA), and then reacting this carrier protein-cross-linker conjugate with a peptide of interest. There is no teaching of a peptide comprising a reactive group, wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group.

Therefore, neither Davidson, nor Peeters, nor Humphries teach the claimed limitation of a kringle 5 peptide comprising a reactive group, wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group.

Applicants contend that the Examiner has not made a *prima facie* case of obviousness against any of the rejected claims, as there is no teaching in the combination of the cited references of the claimed limitation of a kringle 5 peptide comprising a reactive group, wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group.

The second criterion of a *prima facie* case of obviousness is that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The Examiner states, in regards to linking a carrier protein to a kringle 5 peptide using MHS: "One would have been motivated to do so because, as taught by Peeters, et al., MHS is the bifunctional reagent of choice for coupling peptides to proteins because of its low potential for immunogenicity, greater flexibility and greater stability in aqueous solution." There is no suggestion or motivation in any of the cited references to modify a kringle 5 peptide to comprise a reactive group wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group. Instead, as the Examiner points out, the references motivate one of skill in the art to couple a bifunctional reagent to a carrier protein, and then react that carrier protein with a peptide.

The conjugate created by Davidson, et al. between the kringle 5 peptide and BSA, described on page 36, lines 5-9, is created to enable production of polyclonal antisera. Therefore, the kringle 5 peptide-BSA conjugate is immunogenic. This teaches away from the claimed modified peptide of the present invention, which is for therapeutic uses. Therefore an immune response against the conjugate would not only be undesirable, but would interfere with the intended function of the conjugate. Peeters, et al. also teaches the use of the bifunctional reagents for the presentation of an antigen in order to raise antibodies to the peptide of interest in the host. Again, this teaches away from the claimed modified peptide of the present invention. This teaching away would argue against any motivation to combine these refereaces.

Therefore, there is no suggestion or motivation to create the claimed kringle 5 peptide comprising a reactive group, wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group.

The third criterion of a *prima facie* case of obviousness is that there must be a reasonable expectation of success. The Examiner states: "Thus, one of ordinary skill in the art would have a reasonable expectation of success that by using MHS instead of glutaraldehyde as taught by Peeters et al. to link a carrier protein, such as bovine serum albumin, with a kringle 5 peptide, one would achieve a peptide-linked to a carrier protein which upon administration is less immunogenic, more stable and more flexible." The MHS reaction taught by Peeters et al results in the formation of a conjugate of the formula "carrier---LINKER---peptide" as shown in figure 1 of Peeters et al. This reaction would not lead to the formation of a kringle 5 peptide with a reactive group, wherein said reactive group is selected from the group consisting of succinimidyl and maleimido groups. Therefore, there is no reasonable expectation of success.

Based on the above, Applicants respectfully provide that a *prima facie* case of obviousness has not been made, and request the rejection of independent claims 22 and 35, and dependent claims 24-25, 36, 38, 41-43, 45 and 48, be withdrawn.

Claims 28 and 34

The Examiner has rejected claims 28 and 34 as being unpatentable over Davidson, et al. in combination with Peeters, et al. (J. Immunol Methods 1989; 120: 133-143) in view of Yeh, et al. (J. Tissue Culture Methods 1994; 16: 239-242). Specifically, the Examiner states: "It would have been *prima facie* obvious to one of skill in the art at the time the invention was made to use human serum albumin instead of bovine serum albumin as the carrier protein in view of the teachings of Yeh et al."

Again, in order to make a *prima facie* case of obviousness, three criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (MPEP 2142). Applicants contend that Davidson, Peeters and Yeh, when combined, do not teach or suggest all of the claim limitations. Specifically, none of the references teach or suggest a modified kringle 5 peptide wherein said kringle 5 peptide comprises SEQ ID NO: 8 and **a reactive group, wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group**, as claimed in independent claims 22 and 35.

As described above, neither Davidson nor Peeters teach the claimed limitation of a kringle 5 peptide comprising a reactive group, wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group. Yeh, et al. does not teach this claimed limitation either. In fact, Yeh, et al. teaches away from this claimed limitation on page 1904, column 2, which states:

> "However, as pointed out by the authors, the "error nature of the cross-linking procedure" raises important limitations concerning exact formulation and reliability of such pharmaceutical preparations, a problem that should be avoidable by using genetic engineering techniques such that a composite gene encoding a suitable HSA conjugate can be secreted and easily recovered in a homogeneous state."

Therefore, Yeh, et al. does not teach the claimed limitation of a kringle 5 peptide comprising a reactive group, wherein said reactive group is selected from the group consisting of succinimidyl and maleimido groups.

Therefore, Davidson, and Peeters, and Humphries when combined do not teach the claimed limitation of a kringle 5 peptide comprising a reactive group, wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group. Applicants contend that the Examiner has not made a *prima facie* case of obviousness, as there is no teaching in any of the cited references of the claimed limitation of a kringle 5 peptide comprising a reactive group, wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group.

The second criterion of a *prima facie* case of obviousness is that there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. The Examiner states, in regards to using human serum albumin instead of bovine serum albumin as a carrier protein: "One would have been motivated to do so because as taught by Yeh, et al., human serum albumin (HSA) represents an optimal carrier for therapeutic peptides/proteins because of its remarkably long half life, wide *in vivo* distribution and lack of enzymatic or immunological functions." There is no suggestion or motivation in any of the cited references to modify a kringle 5 peptide to contain a reactive group wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group. Instead, combining these references would lead to creating a fusion protein between HSA and a kringle 5 peptide by genetic means, such as cloning. Also, the Yeh, et al. reference teaches the creation of a non-immunogenic fusion protein, whereas the Davidson and Peters references teach the creation of an immunogenic conjugate. The opposite functions of the final products teaches away from the claimed invention and would discourage a combination of these references. Therefore, there is no suggestion or motivation to modify or combine these reference teachings.

The third criterion of a *prima facie* case of obviousness is that there must be a reasonable expectation of success. The Examiner states: "Further, as taught by Yeh, et al., the elimination half-life of the conjugate was increased as compared to the "unconjugated" antibody. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by using human serum albumin as the carrier protein as taught by Yeh et al., one would achieve a peptide conjugate which has greater half-life *in vivo* as compared to the unconjugated peptide." There is no expectation that

this reaction would lead to the formation of a kringle 5 peptide with a reactive group, wherein said reactive group is a succinimidyl-containing group or a maleimido-containing group. Instead, the combination of these references would lead to a fusion protein between HSA and a kringle 5 peptide by genetic means, such as cloning. Therefore, there is no reasonable expectation of success.

Based on the above, Applicants respectfully provide that a *prima facie* case of obviousness has not been made, and request the withdrawal of the rejection of claims 28 and 34.

As stated above, the conjugate created by Davidson et al between the kringle 5 peptide and BSA, described on page 36, lines 5-9, is created to enable production of polyclonal antisera. Therefore, the kringle 5 peptide-BSA conjugate is immunogenic. This teaches away from the claimed modified peptide of the present invention, which is for therapeutic uses. Therefore an immune response against the conjugate would not only be undesirable, but would interfere with the intended function of the conjugate. Peeters et al also teaches the use of the bifunctional reagents for the presentation of an antigen in order to raise antibodies to the peptide of interest in the host. Again, this teaches away from the claimed modified peptide of the present invention.

Therefore, even if a *prima facie* case of obviousness had been made, the fact that the references teach away from the claimed invention leads Applicants to respectfully request the withdrawal of the rejection of claims 28 and 34.

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket

no.500862002200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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